COMPARATIVE STUDY OF SERUM LIPID LEVELS IN PATIENTS OF DIABETIC RETINOPATHY WITH AND WITHOUT CLINICALLY SIGNIFICANT MACULAR EDEMA

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CERTIFICATE

This is to certify that this dissertation entitled **"COMPARATIVE STUDY OF SERUM LIPID LEVELS IN PATIENTS OF DIABETIC RETINOPATHY WITH AND WITHOUT CLINICALLY SIGNIFICANT MACULAR EDEMA"** has been done by **DR.VEENA PRABHU** guidance in Department of OPHTHALMOLOGY, Madurai Medical College, Madurai.

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I, **Dr. VEENA PRABHU** solemnly declare that the dissertation titled **""COMPARATIVE STUDY OF SERUM LIPID LEVELS IN PATIENTS OF DIABETIC RETINOPATHY WITH AND WITHOUT CLINICALLY SIGNIFICANT MACULAR EDEMA"** has been prepared by me.

This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.S.,(Ophthalmology) Branch-III degree Examination to be held in MARCH 2010.

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CONTENTS

INTRODUCTION

Diabetes Mellitus is a major health hazard today. According to World Health Organization, at least 177 million people worldwide suffer from diabetes. It is estimated that there will be rapid increase in the number of persons with diabetes mellitus worldwide. In India, the number shall be 57 million by 2025, compared with 19 million in 1995.

Diabetic retinopathy remains a leading cause of blindness in the world in the age group of 20 to 75 years. Blindness in diabetic retinopathy results from non resolving vitreous hemorrhage, tractional retinal detachment or diabetic macular edema.

As the severity of overall retinopathy increases, the proportion of eyes with macular edema also increases- 30% in mild NPDR, 38% in moderate to severe NPDR and 71% in PDR.

Diabetic maculopathy is a term that encompasses a wide range of intra retinal and pre retinal pathological changes affecting the macula in diabetic retinopathy. The intra retinal changes are composed of two distinct but inter related components:

1. Retinal ischemia due to capillary and arteriolar non perfusion.
2. Retinal edema due to breakdown in the blood retinal barrier.

Diabetic macular edema may be present at any level of retinopathy and alter the structure of macula, significantly affecting its function.

The two major categories of macular edema in diabetic maculopathy are focal macular edema and diffuse macular edema.

Focal macular edema is characterized by areas of focal fluorescein leakage from specific capillary lesions like micro aneurysms, dilated capillary segments and is often associated with hard exudates rings.

Diffuse macular edema presents a much more complex problem than focal macular edema. It is characterized by widespread retinal capillary abnormalities associated with diffuse leakage due to extensive breakdown of blood retinal barrier throughout the posterior pole and often formation of cystoid macular edema.

Effects of diabetes on macula:

1. Macular edema- collection of intra retinal fluid in macula with or without lipid exudation and cystoid changes.

2. Traction in macula by fibrous tissue proliferation causing a dragging of retinal tissue, surface wrinkling or detachment of macula.
2. Intra retinal or pre retinal hemorrhage at macula.
3. Lamellar or full thickness retinal hole formation.

Clinically, macular edema is retinal thickening within two disc diameters from centre of the macula.

Clinically significant macular edema(CSME), as defined by the ETDRS, includes any one of the following lesions:

1. Thickening of retina located within 500 u from centre of macula or
2. Hard exudates with thickening of adjacent retina located within 500 u from centre of macula or
3. A zone of retinal thickening, one disc area or larger in size, located within one disc diameter from centre of macula.

Most patients with DME experience blurred vision, but patients without involvement of centre of macula may have excellent visual acuity and no visual complaints. Once DME develops, treatment is more likely to stabilize vision than to improve it. Hence, it is important to examine asymptomatic diabetic patients regularly

rather than waiting for visual loss to occur, at which time the condition may be more advanced and less responsive to treatment.

There are particular retinal lesions identified on FFA that are amenable to treatment. These ‘treatable lesions’ associated with macular edema include-

a) Focal leaks > 500 u from centre of macula believed to be causing retinal thickening or hard exudates.
b) Focal leaks 300–500 u from the centre of macula believed to be causing retinal thickening or hard exudates, if the ophthalmologist does not believe that treatment is likely to destroy the remaining perifoveal capillary network.
c) Areas of diffuse leakage that have not been treated previously.
d) Avascular zones, other than ‘FAZ’ not treated previously

The ETDRS used 2 types of photo coagulation treatment for DME, focal and grid. Focal refers to direct treatment of all leaking micro aneurysms in the edematous retina, b/w 500-3000u from the centre of macula.

Grid treatment is used primarily for identifiable focal leakage areas and thickened avascular zones.

Elevated lipid levels are associated with endothelial dysfunction, which appears to play an important role in the pathogenesis of DR, particularly in relation to break down of blood retinal barrier and development of CSME and hard exudates. Patients with diabetes are known to have severe lipid abnormalities like hyper cholesterolemia and elevated serum triglycerides. The WESDR, a population based study and the ETDRS found that increased levels of serum cholesterol were associated with increased severity of hard exudates in retina. Independent of accompanying macular edema, the severity of retinal hard exudates at base line was associated with decreased visual acuity in the ETDRS. The severity of retinal hard exudates also was a significant risk factor for moderate vision loss during the course of the study. The data are compelling to recommend lowering raised serum lipid levels in patients with DR to reduce the risk of visual loss besides reducing the risk of cardiovascular disease. However, to our knowledge there is no case control study that has compared the lipid profile levels in subjects with and without CSME.

DIABETES IN A NUTSHELL

Diabetes Mellitus (DM) is a chronic condition that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces.

Hyperglycemia and related disturbances in the body's metabolism can lead to serious damage of many systems especially the nerves and blood vessels.

There are 2 basic forms of DM

1. Type 1 - People with this type of DM produce very little or no insulin. They require daily injections of insulin to survive.
2. Type -2 - People of this type of DM cannot use insulin effectively. This condition can sometimes be managed with life style measures alone but oral drugs are often required and less frequently insulin in order to achieve good metabolic control.

Most people have type 2 DM. Many are symptomless and only diagnosed after many years of onset.

PATHOGENESIS OF DIABETIC RETINOPATHY

Diabetic retinopathy is a micro angiopathy primarily affecting the pre capillary arterioles, capillaries and post capillary venules, although larger vessels may also be involved. It exhibits features of both micro vascular occlusion and leakage.

A. Micro vascular occlusion

Pathogenesis:

1. Capillary occlusion: Consists of loss of pericytes, thickening of basement membrane and damage and proliferation of endothelial cells.
2. Hematological changes: consists of deformation and rouleaux formation of red blood cells and increased platelet stickiness and aggregation, leading to decreased oxygen transport.

Consequence:

Retinal capillary non perfusion leads to retinal ischemia. The effects of this are

1. Arterio venous shunts
2. Neo vascularisation

B. Micro vascular leakage

Pathogenesis:

Breakdown of inner blood retinal barrier leads to leakage of plasma constituents into the retina. Micro aneurysms which are due to physical weakening of the capillary wall are formed, which may leak or get thrombosed.

Consequence:

Increased vascular leakage leads to development of

1. Intra retinal hemorrhages
2. Diffuse retinal edema
3. Localized retinal edema.

CLASSIFICATION OF DIABETIC RETINOPATHY

1. NON PROLIFERATIVE DIABETIC RETINOPATHY (NPDR)

a. Mild NPDR: Micro aneurysms plus retinal hemorrhages, hard exudates.

b. Moderate NPDR: Mild NPDR plus cotton wool spots and/or IRMA.

c. Severe NPDR: Presence of one of the following features.

i. Micro aneurysms plus venous beading and/or hemorrhage/ Micro aneurysms $\geq$ standard photograph 2A in four quadrants.

ii. Marked venous beading in two or more quadrants.

iii. Moderate intra retinal micro vascular anomalies (Standard photographs 8) one or more quadrant.

d. Very severe NPDR: Two or more of the features described in severe NPDR.

2. PROLIFERATIVE DIABETIC RETINOPATHY (PDR)

a. PDR without high risk characteristics

New vessels and/or fibrous proliferation; or pre retinal and/or vitreous hemorrhage.

b. PDR with high risk characteristics

NVD $\geq$ standard photograph 10A; or less extensive NVD if vitreous or pre retinal hemorrhage is present; or NVE $\geq$ half disc area; if vitreous or pre hemorrhages are present.

c. Advanced PDR

Extensive vitreous hemorrhage precluding grading, retinal detachment involving the macula, phthisis bulbi or enucleation secondary to a complication of secondary retinopathy.

RISK FACTORS FOR THE PROGRESSION OF DIABETIC RETINOPATHY

1. **Duration of Diabetes :**

The best predictor of diabetic retinopathy is the duration of the disease. Patients who have had type 1 for 5 years or less rarely show any evidence of diabetic retinopathy. However, 27% of those who have had diabetes for 5-10 years and 71-90% of those who had diabetes for longer than 10 years have diabetic retinopathy. After 20 years, the incidence rises to 95%, and about 30-50% of these patients have proliferative diabetic retinopathy.

Yanko et al described the prevalence of retinopathy in patients with type 2 diabetes. They found that the prevalence of retinopathy 11-13 years after the onset of diabetes was 23%, after 16 or more years, it was 60% and 11 or more years after the onset, 3% of the patients had PDR.

Klein et al found that 10 year after the diagnosis of type 2 diabetes, 67% of patients had retinopathy and 10% had PDR.

2. Effect of control of blood glucose:

The Diabetes Complications and Control Trial (DCCT) showed that patients with type 1 diabetes who had tight blood glucose control do far better than patients treated with conventional therapy. The

former had a 76% reduction in the rate of development of any retinopathy and a 54% reduction in progression of established retinopathy as compared with the conventional treatment group. For advanced retinopathy, however, even the most rigorous control of blood glucose may not prevent progression. The value of intensive treatment has been demonstrated in patients with type 2 diabetes as well.

3. Presence of renal disease:

Renal disease is an excellent predictor of the presence of retinopathy. Even patients with micro albuminuria are at high risk of developing retinopathy. Similarly, 35% of patients with symptomatic retinopathy show evidence of renal disease.

4. Hypertension:

Systemic hypertension appears to be an independents risk factor for diabetic retinopathy. Tight control appears to be particularly beneficial in type 2 diabetes with maculopathy. A study by Chaturvedi et al suggested that there might be a specific benefit of angiotensin converting enzyme inhibition and blood pressure reduction on the progression of diabetic retinopathy.

5. Elevated serum lipid levels:

The WESDR and the ETDRS found that elevated levels of serum cholesterol were associated with increased severity of retinal hard exudates. Elevated levels of serum triglycerides and LDL-C were found to be associated with greater risk of developing PDR.

6. Pregnancy:

Diabetic retinopathy may be accelerated during pregnancy because of pregnancy itself or the changes in metabolic control. Fortunately, there is usually some regression after delivery. The risk of developing NPDR is about 10% and 4% of patients with NPDR progress to PDR.

7. Other systemic risk factors:

Anemia has been reported to be associated with progression of diabetic retinopathy.

History of diabetic neuropathy and cardiovascular autonomic neuropathy has also been suggested to be associated with increased risk of progression of retinopathy.

TREATMENT OF DIABETIC MACULAR EDEMA (DME)

DME is the most common cause of moderate to severe visual loss in patients with diabetic retinopathy. The ETDRS proved that laser treatment reduces moderate visual loss in patients with CSME. Among the ETDRS, in patients with CSME, 33% who were randomized to no treatment had visual loss after 3 years follow up. Focal treatment reduced this frequency by 60% to 13%. CSME requires laser photo coagulation irrespective of visual acuity because treatment reduces the loss of vision loss by 50%.

Mechanism of action of laser in DME:

1. Focal burns appear to coagulate the leaking micro aneurysms or the retinal vessels in the inner and middle retina which cause DME They stop leaking and result in improvement in DME.

2. Damage to the outer blood retinal barrier causes the elaboration of a substance that in turn, causes mitosis of endothelial cells. After treatment, the vessels leak less and/or absorb more affecting a reduction of DME and accompanying hard exudates.

3. Laser treatment destroys some of the photo receptors and retinal pigment epithelial cells which are the layers which consume most of the oxygen used by the retina. Post treatment scarring also causes

retinal thinning which allows for better diffusion of oxygen from the choroids. After laser treatment, oxygen consumption of the retina is reduced and the supply to thin retina from the choroid is increased.

4. Retinal capillaries, especially in patients with severe DME, are often dilated before treatment and become narrower and less leaky after laser treatment.

The techniques of laser treatments in DME are:

a. **Focal treatment:** Involves application of laser burns to the micro aneurysms and micro vascular lesions in the centre of rings of hard exudates located 500 to 3000 micrometers from the centre of the macula. The spot size is 50-100 micrometers and exposure time of 0.1 seconds with sufficient power to obtain gentle whitening or darkening of the lesions. Treatment up to 300 micrometers from the centre of the macula may be considered if CSME persists despite previous treatment and visual acuity is < 6/12. In these cases a shorter exposure time of 0.01 seconds is recommended.

b. **Grid treatment**: It is used for areas of diffuse retinal thickening located more than 500 micrometers from the centre of the macula and 500 micrometer from temporal margin of the optic

disc. The spot size is 100 micrometers and exposure is 0.1 second giving a very light intensity burn and one burn width apart.

Approximately 70% of eyes achieve stable visual acuity, 15% show improvement and 15% subsequently deteriorate. Since it may take up to four months for the edema to resolve, retreatment should not be considered prematurely.

Other forms of treatment:

1. Pars Plana Vitrectomy may be indicated when macular edema is associated with tangential traction from a thickened and taut posterior hyaloid. In these cases, laser is of limited benefit but surgical release of traction may be beneficial. OCT is invaluable in demonstrating eyes with marked vitreoretinal traction that may benefit most from surgery.
2. Intra vitreal triamcinalone acetonide may be tried for the treatment of diffuse macular edema that fails to respond to conventional laser photocoagulation. Its complications include endophthalmitis, intra ocular hemorrhage, retinal detachment and increased intra ocular pressure. The therapeutic effect fades after six months and macular edema frequently returns.

3. Posterior subtenon triamcinalone acetonide may improve visual outcome in diffuse macular edema when combined with laser photo coagulation but long term results are lacking.
4. Anti VEGF agents are also under study for treatment of DME .
5. Hypo lipidemic drugs have been shown to reduce the severity of hard exudates and sub foveal lipid migration in eyes with CSME in type 2 diabetes mellitus patients with dyslipidemia and may become an important therapeutic adjunct.

OVERVIEW OF LIPIDS

Lipids are a heterogeneous group of water insoluble organic molecules that can be extracted from tissues by non polar solvents. Due to their insolubility in aqueous solutions, body lipids are generally found either compartmentalized, as in case of membrane associated lipids and droplets of tryglycerides in adipocytes, or transported throughout the body in association with proteins as lipoprotein particles. These particles include chylomicrons , very low density lipoprotein(VLDL) , low density lipoprotein(LDL) and high density lipoprotein(HDL).

Lipoproteins are spherical particles made up of hundreds of lipid and protein molecules, smaller than RBC’s are seen only by electron microscope. Major lipids present in lipoproteins are cholesterol, triglycerides and phospholipids. Triglycerides and the esterified form of cholesterol (Cholesteryl ester) are non polar and hydrophobic and comprise the lipoprotein core. Phospholipids and small quantities of free cholesterol which are soluble in both aqueous and lipid envelop (amphipathic) cover the surface of the particle, where they act as interface between plasma and core components.

A very important lipid is cholesterol. It is an alicyclic compound whose structure includes basically a perhydrocyclopentenophenantheren nucleus with its four fused rings. Cholesterol has very low solubility in water. The actual concentration of cholesterol in the plasma of healthy people is usually 150-200mg/dl. The very high solubility of cholesterol in blood is due to proteins called plasma lipoproteins (mainly LDL and VLDL) that have the ability to bind and thereby solubilise large amounts of cholesterol.

Only 30% of total circulation cholesterol occurs free as such, around 70% of the cholesterol in plasma lipoproteins exist in the form of cholesterol esters.

Cholesterol is abundant in bile. Solubilisation of free cholesterol in bile is achieved by the detergent property of the phospholipids present in bile that are produced in the liver.

Cholesterol, which can be derived from diet are manufactured de novo in virtually all human cells plays very important role. It is a major sterol in virtually all plasma and intra cellular membranes. It is especially abundant in the myelinated structures of the brain and the CNS. Most of the cholesterol in cellular membranes occurs in free

form. It is the immediate precursor of bile acids, that are synthesized in the liver and that function to facilitate the absorption of dietary triglycerides and fat soluble vitamins. It is also the precursor of various steroid hormones.

Cholesterol biosynthesis is carefully regulated. When dietary cholesterol is reduced, cholesterol synthesis is increased in liver and intestine. Cholesterol synthesized de novo is transported from liver and intestine to peripheral tissues in the form of lipoproteins. Only these two tissues can manufacture apolipoprotein D, the protein component of cholesterol transport proteins LDL and VLDL. Highest proportion of cholesterol is found in LDL. Most of the apo B is secreted into the circulation as VLDL, which is converted in LDL but removal of triglycerol and the apo C components, probably in peripheral tissues and liver. In contrast when the quantity of dietary cholesterol increases, synthesis is almost totally suppressed.

Virtually all tissues containing nucleated cells are capable of synthesizing cholesterol. Synthesis takes place in several stages. The primary site for control of cholesterol biosynthesis is HMG COA reductase, which catalyses the step that produces mevalonic acid. This

is a committed step and the rate limiting reaction in the pathway of cholesterol biosynthesis.

HYPERLIPOPROTEINEMIAS:

Broadly classified as:

1. **Isolated hypercholesterolemia:**

   Increased levels of fasting total plasma cholesterol, in presence of normal levels of triglycerides, is almost always associated with increased levels of plasma LDL-C(type II a) as LDL carries 65-75% of total cholesterol.

2. **Isolated triglyceridemia:**

   The diagnosis of hypertriglyceridemia is made by determining levels of plasma lipids after an overnight fast. Isolated elevation of plasma triglycerides can be due to increased levels of VLDL (type 4) or a combination of VLDL and chylomicrons (type 5)

3. **Hypertriglyceridemia and Hypercholesterolemia**

   Combination of the conditions can also occur.

Classification of Total cholesterol, LDL Cholesterol and HDL Cholesterol values:

	Total cholesterol	LDL-C	HDL-C
Desirable	5.2 mmol/l	<3.36 mmol/l	>1.55 mmol/l
	<200 mg/dl	<130 mg/dl	>60 mg/dl
Borderline	5.5-6.18 mmol/dl	3.36-4.14 mmol/dl	0.9-1.55 mmol/dl
	200-239 mg/dl	130-159 mg/dl	35-60 mg/dl
Undesirable	≥6.21 mmol/l	≥4.41 mmol/l	≤0.9 mmol/l
	≥240 mg/dl	≥160 mg/dl	≤35 mg/dl

The correlation between high levels of blood cholesterol, particularly LDL cholesterol and heart attacks and strokes have led to the development of dietary and therapeutic approaches to lower blood cholesterol.

Treatment of dyslipidemias:

Non Pharmacological Treatment :

Diet and dietary modification is an important component in the management of dyslipidemias. The physician should assess the content of the patient's diet and provide suggestions for dietary

modification. Other modifications of lifestyle include cessation of smoking, cutting down alcohol intake, weight reduction if appropriate and regular exercises.

Pharmacological Treatment :

1. HMG COA reductase inhibitors (statins): HMG COA reductase in the rate limiting step in cholesterol biosynthesis and inhibitors of this enzyme decreased cholesterol synthesis. It causes dose dependent reduction in plasma levels of LDL & TGs and increase in HDL. Statins are remarkably safe and well tolerated. Potential side effects include dyspepsia, headache, fatigue muscle or joint pain and rarely severe myopathy and rhabdomyolysis.

Eg. Lovastatin, Provastatin, Snvastatin, Fluvaslatin, Atorvastatin, Rosuvastatin.

2. Cholesterol absorption inhibitors:

Ezetisube is a cholesterol absorption inhibitor that binds directly to a protein NPC ILI and blocks the intestinal absorption of cholesterol. It has been shown to decreased cholesterol also by almost 60%. It can be used in combination with statins.

3. Bile Acid sequestrants (Resins) : BAS

Bind bile acids in the intestine and promote their excretion. To maintain bile acid pool size, the liver diverts cholesterol to bile acid synthesis.

Eg. Cholestyramine, colestipol, colesevelam

4. Nicotinic Acid (Niacin):

Niacin is a lipid modifying agents with decreased plasma TG and LDL levels and increased HDL – C. It is also the only currently available lipid lowering agent that significantly reduces plasma levels of LP(a)

5. Fibric acid derivatives (Fibrates):

FAD are agonists of PPAR alpha, a nuclear receptor involved in the regulation of carbohydrate and lipid metabolism. Fibrates are the most effective drugs available for reducing TG, VLDL and increased HDL C

6. Omega 3 Fatty Acids (Fish oils)

Polyunsaturated fatty acids are present in high concentrations in fish and in flax seeds, Low dose of Omega 3 has been also decreased fasting TG levels and reduction in cardiovascular events in CHD patients.

REVIEW OF LITERATURE

There are conflicting reports in literature regarding the lipid profile in diabetics. Some workers have found elevated levels of cholesterol and no difference was observed in serum phospholipids between diabetics with and without retinopathy. Lopes – Virella *et al* found inverse correlation between HDL-C with poorly controlled diabetics. Few reports suggest that there is significant increase in cholesterol, phospholipids and triglycerides in diabetics with retinopathy as compared to controls.

Emily. Y. Chew et al studied observational data from ETDRS and evaluated the relationship between serum lipid levels, retinal hard exudates and visual acuity in patients with diabetic retinopathy. They concluded that patients with elevated total serum cholesterol levels and serum LDL-C at baseline where twice as likely to have retinal hard exudates as patients with normal levels. The risk of losing visual acuity was associated with the extent of hard exudates. The observational data from ETDRS suggest that lipid lowering may also decrease the risk of hard exudates formation and associated visual loss in patients with diabetic retinopathy.

Barbara.E.Klein et al did a study of the cohort of younger onset diabetes mellitus group in Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) to determine whether relationship exists among the serum lipid levels and severity of diabetic retinopathy, retinal hard exudates and macular edema 5 years later. Their data suggested that lowering cholesterol levels by diet or pharmacological means was not indicated for the sole purpose of reducing the incidence or severity of retinal lesions.

Klein R, Klein B.E.K et al measured serum total and HDL-Cholesterol in a sample of individual in WESDR. It showed a significant trend for increasing severity of diabetic retinopathy and of retinal hard exudates with increasing cholesterol in insulin using persons. However, no relationship was found between total cholesterol and severity of hard exudates in the older onset group that did not use insulin. They concluded that different pathogenic mechanisms may be associated with the development of hard exudates in people who have different type of diabetics.

S.P.Dhir, Rajvir Dahiya et al in a study done in North India of the lipoprotein profile in diabetic patients with and without diabetic retinopathy did not reveal any significant difference though all the

values were slightly elevated in diabetic retinopathy group as compared to diabetics without retinopathy.

A number of recent cross sectional studies suggest that serum lipids may have a causative role in macular exudates. Comparison of a small group of diabetic patients with severe exudative maculopathy to a group of non exudates retinopathy by Brown GC et al demonstrated significantly higher levels of triglycerides in the formal group, although serum cholesterol was not significantly different. A case control study by Dodson PM et al where patients were matched for age, gender, glycemic control, duration and treatment of diabetes mellitus, found a trend for patients with maculopathy to have higher serum lipids over seven years follow up than patients without. An elevation in cholesterol has been shown in study of exudative maculopathy in type 1 diabetes mellitus by Miccoli R et al.

Further studies have linked LDL-Cholesterol with maculopathy, although number of patients in these studies has been small. A direct toxic effect of LDL on retinal capillary pericytes has also been demonstrated, and this toxic effect can be enhanced by LDL glycation or oxidation. In other small cross sectional studies, lipoprotein (a) has been suggested as a risk factor for maculopathy, although this finding

was refuted on examination of a small subset of the WESDR population. Improved outcome following laser photo coagulation therapy for macular edema has been reported in subjects who have higher HDL-C or normal total cholesterol by Kremser BG et al.

The role of dietary fat intake and its influence on exudative maculopathy has been examined. Ernst et al reported reduction in retinal exudates in eight diabetic patients after 2-3 years of carbohydrate rich, fat poor diet. Seven year follow up of the cohort of 149 patients randomized to a low carbohydrate or a modified fat diet showed that patients with low levels linoleic in cholesterol ester had greater risk of retinopathy.

Stronger evidence for a role of serum lipids in exudative maculopathy is suggested in prospective studies. In the ETDRS a study group of patients had serum lipid measured. Higher baseline total and LDL-C levels increased the risk of retinal exudation by two fold. On multivariate analysis, risk of losing visual acuity was associated with severity of hard exudation. In further analyses, increased serum cholesterol at baseline increased the risk of visual loss by 50% compared to lower serum cholesterol levels. These findings have been supported by examination of a sub group of the

WESDR cohort. Increased total cholesterol was noted in patients with increased severity of retinopathy and hard exudates.

Lipid lowering therapy in exudative maculopathy:

Trials of clofibrate and atromid in exudative maculopathy have suggested that a reduction in macular hard exudates could be achieved, but with little improvement in visual acuity. Of note, however, is that the visual acuity of the patients in these trials was poor at the outset , and hence a significant improvement with lipid lowering therapy may not be expected. A more recent German pilot study used etofibrate in patients with type 2 diabetes and type 2b hyperlipoproteinemia with diabetic maculopathy. Clear regression of macular exudates was seen in seven of ten patients in six months. Two small pilot studies have used statin therapy in diabetic retinopathy. In one pilot study six patients with exudative maculopathy were treated with pravastatin which lowered their total and LDL cholesterol by 40%. Over one year, an improvement in hard exudates was seen in all patients, with decreased micro aneurysms in four patients was observed and visual acuity improved in one patient.

AIMS AND OBJECTIVES

AIM OF THE STUDY:

The aim of this study is to compare the serum lipid profile in patients with diabetic retinopathy with clinically significant macular edema and without clinically significant macular edema.

OBJECTIVES:

1. To study the serum lipid profile in patients with diabetic retinopathy.
2. To compare the serum lipid profile of patients with and without clinically significant macular edema.
3. To compare and analyse the present study with reference to other studies on serum lipid profile in diabetic retinopathy.
4. To emphasize the importance of doing serum lipid profile as a routine investigation in patients with diabetic retinopathy.

MATERIALS AND METHODS

The study group:

The study was conducted on patients with diabetic retinopathy visiting department of ophthalmology at Government Rajaji Hospital, Madurai.

Period of Study:

The study was conducted for a period of one year from June 2008 to May 2009.

Inclusion Criteria:

Patients with diabetic retinopathy who are willing to participate in the study and have given consent to undergo blood tests for serum lipid levels and renal parameters.

Exclusion Criteria:

1. Patients who have had treatment for diabetic retinopathy
2. Patients on treatment for dyslipidemias.
3. Patients not willing to participate in the study.

Sample size:

100 patients divided in to two groups of 50 each.

Group A: Patients with diabetic retinopathy with clinically significant macular edema.

Group B: Patients with diabetic retinopathy without clinically significant macular edema.

Selection of study subjects:

Fifty consecutive patients each of Group A and Group B presenting to ophthalmology outpatient department and those referred from other departments with diabetic retinopathy fulfilling the inclusion criteria of the study.

Methods:

A detailed history was elicited from the patient about the duration of diabetes mellitus, history of treatment, presence of other systemic conditions like hypertension and renal disease.

Anterior segment evaluation was done by slit lamp examination. After dilatation of the pupil with tropicamide eye drops, fundus examination was done using direct ophthalmoscopy, indirect ophthalmoscopy and slit lamp biomicroscopy with +90D lens. Appropriate fundus photographs were taken. Diabetic retinopathy was classified according to ETDRS classification.

All patients were advised overnight fasting and blood sample was taken for estimation of fasting blood glucose, serum lipid levels,

blood urea and serum creatinine. Systolic and Diastolic Blood pressure were measured in sitting posture.

Total cholesterol levels in serum were measured using Libermann Burchard reaction.

RESULTS AND OBSERVATIONS

Group A : Patients with clinically significant macular edema

Group B : Patients without clinically significant macular edema

Table -1: Age Distribution of Cases

Age groups (in years)	Group A		Group B	
	No.	Percentage	No.	Percentage
Up to 50 yrs	9	18	8	16
51 -60	21	42	23	46
61 – 70	13	26	16	32
> 70	7	14	3	6
Total	50	100	50	100
Range	39 – 87 yrs		42 – 77 yrs	
Mean	59.7 yrs		58.8 yrs	
S.D	9.7		7.8	
P	0.6762 Not significant			

The age of the patients in the study ranged from 39- 87 years. Patients with CSME had mean age of 59.7 yrs and without CSME 58.8. Age was not found to be significantly related to the presence of CSME.

Table -2: Sex Distribution of Cases

Sex	Group A		Group B	
	No.	Percentage	No.	Percentage
Male	26	52	24	48
Female	24	48	26	52
Total	50	100	50	100
P	0.8415 Not significant			

Males slightly predominated the group with CSME with 52% and females in the group without CSME.

Table -3: Duration of DM

Duration of DM (in years)	Group A		Group B	
	No.	Percentage	No.	Percentage
Newly detected	6	12	8	16
Up to 5 years	13	26	32	64
6 – 10 years	10	20	6	12
11 – 15 years	14	28	2	4
> 15 years	7	14	2	4
Total	50	100	50	100
P value (< 10 yrs to > 10yrs)	0.0002 Significant			

Up to 28% of the patients with CSME had type 2 Diabetes Mellitus for duration ranging from 11-15 yrs whereas majority of the patients without CSME had Diabetes Mellitus for up to 5 years comprising 64% of the total.

Table -4: Drugs

Drugs	Group A		Group B	
	No.	Percentage	No.	Percentage
Yes	39	78	35	70
No	11	22	15	30
P	0.494 Not significant			

Among the patients with CSME, 78% were on treatment and 70% among the patients without CSME were on treatment for Diabetes Mellitus. Treatment history was not found to be significantly related to presence or absence of CSME.

Table -5: Severity of Diabetic Retinopathy

Type of DR	Right Eye				Left Eye			
	A		B		A		B	
	No.	%	No.	%	No.	%	No.	%
No DR	4	8	9	18	10	20	10	20
Mild NPDR	14	28	20	40	16	32	26	52
Moderate NPDR	16	32	13	26	12	24	8	16
Severe NPDR	7	14	3	6	4	8	2	4
PDR	7	14	3	6	4	8	2	4
Total	50	100	50	100	50	100	50	100

Majority of the patients with CSME had moderate NPDR whereas patients without CSME had a higher percentage of mild NPDR in either or both eyes.

Table -6: Clinically significant macular edema

CSME	Right Eye				Left Eye			
	A		B		A		B	
	No.	%	No.	%	No.	%	No.	%
Yes	37	74	0	0	33	66	0	0
No	13	26	50	100	17	34	50	100

Among the patients who had CSME, it was more common in right eye in our study at 74% than in left eye.

B: Relationship between Lipid Profile and incidence of CSME in patients with Diabetic Retinopathy

Table -7: Total cholesterol and CSME

Total Cholesterol	Group A		Group B	
	No.	Percentage	No.	Percentage
Normal (<200)	13	26	37	74
Abnormal (>200)	37	74	13	26
Range	140 – 516		114 – 408	
Mean	268.6		193.5	
SD	82.0		71.2	
P	0.0001 Significant			

Total cholesterol levels in patients of Group A ranged from 140 – 516 mg/dl with a mean of 268.6 mg / dl and Group B from 114 – 408 mg / dl with a mean of 193.5 mg / dl. Total cholesterol level was found to be statistically significant with a ‘p’ value of 0.0001.

Table -8: TGL and CSME

TGL	Group A		Group B	
	No.	Percentage	No.	Percentage
Normal (< 160)	18	36	31	62
Abnormal (>160)	32	64	19	38
Range Mean SD	98 – 318 173.9 40.8		76 – 341 149.2 47.3	
P	0.0013 Significant			

Patients with CSME were found to have higher triglyceride levels with a mean of 173.9 mg / dl compared to patients without CSME who had a mean triglyceride levels of 149.2 mg/dl with the ‘p’ value of 0.0013, increased triglyceride levels were found to be significantly related to presence of CSME.

Table -9: HDL and CSME

HDL	Group A		Group B	
	No.	Percentage	No.	Percentage
Normal (< 35)	17	34	32	64
Abnormal (>35)	33	66	18	36
Range	12 – 56		20 – 44	
Mean	29.5		34.4	
SD	8.5		6.2	
P	0.0007 Significant			

Patients in group A had mean HDL-C levels of 29.5 mg/dl and group B of 34.4 mg / dl. Decreased serum HDL-C level was found to be significantly related to the presence of CSME.

Table -10: LDL and CSME

LDL	Group A		Group B	
	No.	Percentage	No.	Percentage
Normal (< 160)	16	32	38	76
Abnormal (>160)	34	68	12	24
Range	84 - 402		54 – 300	
Mean	187.2		119.5	
SD	62.5		54.3	
P	0.0001 Significant			

Patients in group A had higher serum LDL-C levels with a mean of 187.2 mg / dl compared to patients in group B with 119.5 mg% which was found to be statistically significant.

Table -11: VLDL and CSME

VLDL	Group A		Group B	
	No.	Percentage	No.	Percentage
Normal (< 40)	20	40	39	78
Abnormal (>40)	30	60	11	22
Range	16 – 110		9 – 130	
Mean	51.9		38.6	
SD	24.9		22.4	
P	0.0069 Significant			

Patients in both the groups were found to have higher than normal levels of serum VLDL-C with Group A having a mean of 51.9 mg / dl and group B a mean of 38.6 mg / dl which was found to be statistically significant.

Table -12: Blood Urea and CSME

Blood Urea	Group A		Group B	
	No.	Percentage	No.	Percentage
Normal (< 40)	23	46	36	72
Abnormal (>40)	27	54	14	28
Range	16 – 64		17 – 70	
Mean	41.2		33.6	
SD	15.8		12.4	
P	0.0115 Significant			

Patients with CSME had higher blood urea level compared to patients without CSME

Table -13: Serum Creatinine and CSME

Serum Creatinine	Group A		Group B	
	No.	Percentage	No.	Percentage
Normal (< 1.2)	18	36	33	66
Abnormal (>1.2)	32	64	17	34
Range	0.6 – 4.4		0.6 – 4.3	
Mean	1.43		1.32	
SD	0.7		0.89	
P	0.0142 Significant			

Patients with Diabetic retinopathy in general were found to have increased serum creatinine levels with mean value being 1.43 mg/dl and 1.32 mg /dl in group A and group B respectively.

Table -14: Blood Pressure and CSME

TGL	Group A		Group B		'p'
	Mean	SD	Mean	SD	
Systolic BP	18	36	31	62	0.0001 Significant
Diastolic BP	86	6.9	83.7	8.1	0.051 Not significant

Patients in both the groups had higher than normal systolic BP whereas diastolic blood pressure was normal in either group.

Table -15: Fasting Blood Sugar and CSME

	Group A		Group B	
	No.	Percentage	No.	Percentage
Normal (< 126)	18	36	30	60
Abnormal (>126)	32	64	20	40
Range	24 – 314		43 – 306	
Mean	154.3		129.3	
SD	53.0		50.0	
P	0.0182 Significant			

Patients with CSME had a higher mean fasting blood sugar levels than patients without CSME which was found to be statistically significant with a ‘p’ value of 0.0182.

Table -16 Abstract

Parameters	Group A		Group B		'p'
	Normal	Abnormal	Normal	Abnormal	
Total cholesterol	13	37	37	13	0.0001 Significant
TGL	18	32	31	19	0.0013 significant
HDL	17	33	32	18	0.0007 significant
LDL	16	34	38	12	0.0001 significant
VLDL	20	30	39	11	0.0069 significant
Blood Urea	23	27	36	14	0.0015 significant
Serum Creatinine	18	32	33	17	0.00142 significant
FBS	18	32	30	20	0.0182 significant

DISCUSSION

Diabetic retinopathy is one of the leading causes of blindness in people aged 20 to 74 years. Macular edema is the most frequent cause of visual impairment in patients with diabetic retinopathy. There are several contradictory reports in literature regarding the lipid profile in diabetic retinopathy and its relationship with the presence of retinal exudates. There have been many studies done which compare the lipid profile in diabetic retinopathy and its relationship with the presence of retinal exudates. But not many studies have been done which compare the lipid profile in subjects with and without CSME. This study is a comparative study of serum lipid profile in diabetic patients with and without CSME.

Most of the observations made in this study correlated with the world literature. Several studies in the past have suggested that the prevalence of diabetic retinopathy increases with duration of diabetes mellitus. Only 12-16% of the newly detected diabetes in our study showed diabetic retinopathy changes. Most of it was mild NPDR and present in only one eye. The presence of diabetic retinopathy changes in newly detected diabetics could also be attributed to late detection of diabetes mellitus in our population. About 42% of patients with

CSME had diabetes for more than 10 yrs compared to 8% of the patients without CSME. The significance of duration of diabetes is evident from the fact that it correlated very well with the presence of CSME (p=0.0002). It had a good negative predictive value in patients with less than 10 years of diabetes mellitus.

The age and sex distribution was not found to be significant in our study with a ‘p’ value of 0.6762 and 0.8415 respectively. Data from the WESDR has shown clearly that duration of diabetes mellitus is more important factor for the development of CSME and diabetic retinopathy than the age of onset of diabetes.

The relationship of glucose control and severity of diabetic retinopathy has been studied extensively in observational studies. These studies all demonstrated that increased severity of diabetic retinopathy is associated with poorer blood glucose control. Our study showed that both patients with and without CSME had higher than normal fasting blood glucose levels. This observation is in concurrence with the Diabetes Control and Complications Trial and Early Treatment Diabetic Retinopathy Study which showed tight that blood glucose control with intensive insulin or conventional treatment was associated with a decreased risk of either the development or

progression of diabetic retinopathy. In the United Kingdom prospective Diabetes study (UKPDS) the largest and longest study of patients with type 2 diabetes, there was a 25% reduction in the progression of diabetic retinopathy in the intensive treatment group compared to the conventional treatment group. Among the patients with diabetic retinopathy, it was found that patients with CSME had a higher mean blood sugar levels at 154.3 mg/dl compared to patients without CSME. With a ‘p’ value of 0.0182, it is clear that higher fasting blood glucose levels are significantly associated with presence of CSME. Our study also showed that there was not much difference in the risk of developing CSME among the patients who were on treatment compared to those who were not on treatment. Since most of our patients were referred to us from Diabetology department for review, they were found to be on some kind of treatment for diabetes, either in the form of oral anti hyperglycemic drugs or insulin. But despite treatment, most patients did not have adequate blood glucose control. It showed that they need more frequent tests for blood glucose monitoring and more intensive therapy to achieve normoglycemic status.

Out of the 200 eyes of 100 patients studied, 89 eyes had moderate NPDR or more severe forms of diabetic retinopathy. 54 (60%) of these eyes had CSME compared to 35 (40%) which did not have CSME. Though it was not found to be statistically significant, it is still evident that eyes with CSME had more severe forms of diabetic retinopathy.

Our study also showed that severity of diabetic retinopathy increased with the increased duration of diabetes. This is in accordance with previous studies. In the WESDR, it was found that in type 1 diabetes, prevalence of retinopathy was seen in 13% patients with less than 5 year duration of diabetes. Proliferative diabetic retinopathy was rarely found in this group. However, the prevalence increased as duration of diabetes increased and 90% of patients had diabetic retinopathy in patients with duration of 10-15 years and approximately 25% of these patients had FDR. For patients with type 2 diabetes, 24-40% of patients had diabetic retinopathy with duration of less than 5 years with PDR constituting 2% of the total. These rates increased to 53-84% respectively with increased diabetes duration of 15 to 19 years. PDR formed 25% of total patients.

A number of recent cross sectional studies suggest that serum lipid profile may have a causative role in macular edema. A study by Emily Y. Chew et al, who studied the data from ETDRS, concluded that patients with elevated total serum total cholesterol levels and serum LDL-c levels had two times increased risk to have retinal hard exudates than patients who have normal levels.

Our study showed that patients with CSME had significantly elevated total cholesterol levels at a mean of 268.6 mg/dl. Patients without CSME had slightly lower levels but it was in the high normal range. The difference between the two was statistically significant (p=0.0001). But these results are in contrast with a study done by Klein R et al who inferred that there was no relationship between total cholesterol and severity of hard exudates in type 2 diabetes that did not use insulin though there was a treated for increasing severity of diabetic retinopathy and retinal hard exudates with increasing cholesterol levels in type 1 diabetes.

A study done by S.P. Dhir, Rajvir Dahiya et al in North India about Serum Lipoprotein cholesterol profile in diabetic retinopathy showed that there was no significant difference though all the values were slightly elevated in diabetic retinopathy group. But study done

by Macoli F, Odello G et al clearly showed that there was an increase in serum total cholesterol levels in patients with exudative maculopathy in type 1 diabetes patients.

Higher than normal levels of serum triglyceride levels were found in patients with CSME in our study compared to patients without CSME. This is in concordance with the study done by Brown GC et al who demonstrated higher level of triglyceride in patients with exudative maculopathy compared to patients without exudative maculopathy. However, the serum total cholesterol levels was not significantly difference among the two groups. A recent study done in Chennai by Rama M, Srivastava BK et al concluded that there is a significant association of serum triglyceride with diabetic retinopathy but there was no significant association with diabetic macular edema.

The same study found that there was significant association of serum LDL cholesterol with diabetic macular edema. This finding is supported by our study which showed 68% of patients with CSME had abnormal levels of serum LDL-c level compared to only 24% of patients without CSME. Significant association of LDL-c levels with CSME is also evident with CSME is also evident in the ETDRS which showed that higher baseline total and LDL-C levels increased

the risk of retinal hard exudates formation by two times. It also showed that these patients had an increased risk of visual loss by 50% compared with patients with normal levels. Studies by Mohan R et al and Dornanth et al have also showed that increase in serum LDL C levels is associated with increased risk of maculopathy.

A study done by Timethy JL. et al on a subclass in DCCT / EDIC cohort, concluded that severity of retinopathy was positively associated with triglyceride and VLDL levels and negatively associated with HDL-C levels. Our study showed that 60% of patients with CSME had increased serum VLDL –C levels compared to 22% patients without CSME. Similarly, 66% of patients in Group A had lower than normal HDL – C levels as against 36% patients in Group This finding supports the study by Lopes Virella et al who observed a inverse correlation between HDL-C and poorly controlled diabetic retinopathy. But a recent study done in Turkey by Ozer PA et al found no correlation between serum lipid levels and macular edema, but the duration of diabetes was demonstrated as a significant factor in the progression of macular edema. They also found a high HbA1C levels in all the patients which highlighted the importance of intense glycemic control.

Our study also showed that patients with CSME had increased renal parameters in the form of high levels of blood urea and serum creatinine. Patients with CSME also showed higher systolic blood pressure although diastolic blood pressure was not found be significantly different among the two group. This is in accordance to the previous studies which showed that systemic hypertension and renal disease were associated with progression of diabetic retinopathy. But there have not been any studies linking renal disease and systemic hypertension to presence or absence or severity of macular edema. Further evaluation is needed in this regard.

SUMMARY

The study “Comparative study of Serum Lipid Profile in patients with diabetic retinopathy with and without clinically significant macular edema” was a case control study of 100 patients with diabetic retinopathy at Ophthalmology department of Government Rajaji Hospital, Madurai.

Patients who satisfied the inclusion criteria were interviewed regarding the duration of diabetes mellitus and treatment history. Fundus examination was done using direct ophthlmoscopy, indirect ophthalmoscopy, slip lamp biomicroscopy with +90D lens and fundus photographs were taken. Systolic and diastolic blood pressure was recorded. They underwent investigations like, FBS, serum lipid profile, blood urea and serum creatinine levels. The above said variables were compared between the two groups.

There was no significant difference in Age and Sex distribution between the two groups. The present study showed that there were significantly higher levels of fasting blood sugars, serum lipids, blood

urea and serum creatinine among the patients with CSME compared to those without CSME. Both the groups were found to have higher systolic blood pressure levels but it was significantly increased in patients with CSME. Diastolic blood pressure was found to be within normal range both the groups.

CONCLUSION

The present study clearly shows that there is significant correlation between higher levels of serum total cholesterol, LDL-C, VLDL-C and triglycerides and presence of clinically significant macular edema.

CSME is also associated with presence of renal disease and hypertension.

The presence of exudative maculopathy is not currently an indication for institution of lipid lowering therapy. Recent advances in lipid lowering therapy have presented us with the opportunity to intervene effectively in dyslipidemias. While improving antihyperglycemic and anti hypertensive therapy is likely to reduce the incidence of maculopathy, reducing the progression of exudative maculopathy to severe visual loss must also be considered a priority and lipid lowering therapy has the potential to augment losses.

BIBLIOGRAPHY

1. BAIGENT C et al : Efficacy and safety of cholesterol lowering : Prospective mula analysis of data from 90,056 participants in 14 randomised trials of statins lancet 366 : 1267, 2005.
2. BRUNZELL ID : Clinical practice hypertriglyceridemia. N. Engl J Med 357 (10) : 1009, 2009.
3. CANNON CP et al : Intensive Vs Mod. Lipid lowering with statins after acute coronary syndromes. N Engl J Med. 350 : 1495, 2004
4. CARLSON LA : Nicotinic acid : The broad spectrum lipid drug A 50th Anniversary Review. J Intern Med. 258 : 94, 2005.
5. DUFFY D, RADER DT : Emerging therapies targeting high density lipoprotein metabolism and reverse cholesterol transport. Circulation 113 : 1140, 2006.
6. LAROSA JC et al : Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 352 : 1425, 2005.

7. SINGH IM et al : High density lipoprotein as a therapeutic target : A systematic review. JAMA 298 (7) : 786, 2007.

8. Emily Y. Chew et al, Arch Ophthalmolgy 1996, 114 : 1079 – 1084.

9. Barbara E.K. Klein et al, Association of elevated serum lipid levels with Retinal Hard exudates in DR. AM J ophthalmology 1999 ; 128 : 652 – 654.

10. Klein R et al, The WESDR XIII Relationship of serum cholesterol to retinopathy and hard exudates. Ophthalmology 1991 ; 98 : 1261 – 1268.

11. Brown GC, Ridley M, Haas D, Hicer AC, Sarin LK, Leparemic diabetic retinopathy, Ophthalmology 1984 ; 91 : 1490-1495.

12. Dodson PM, Gibson JM, Long term follow up of 8 underlying medical conditions in patient with diabetic exudative maculopathy. Eye 1991 ; 5 : 69-70.

13. Miccoli R, Odello G, Penno G et al, Circulating lipid levels and severity of DR in type 1 DM. Ophthalmic Res. 1987 ; 19 : 52-56.

14. Mohan R. Sushula L, Ramachandran A et al. Increased LDL cholesterol in non insulin dependent diabetes with maculopathy. Acta diabetes hal 1984 ; 21 : 85-89.
15. Dornan TL, Mann JJ et al how density hypoprotein cholesterol : an association with the severity of DR. Diabetologia 1982 : 22 : 167-170.
16. Gueria B, Meyer L, Sommer S et al Severity of DR is linked to lp cas in type in diabetes. Diabetes mehab 1999 ; 25 : 412-418.
17. Kim CH, Park HJ, Park Jy, Lee KU et al. High serum Lp (a) levels in Korean type 2 diabetes patients with PDR diabetes core 1998, 21 : 2149-51.
18. Haffner SM, Klein BE, Moss SE, Klein R. LP (a) is not related to retinopathy in diabetic subjects Eur J Ophthlmol 1995 ; 5 : 119-123.
19. Knemser BG, Falk M, Kreselbaouch, GF. Influence of serum lipid fractions on the course of DME after protocoagulation, ophthalmolgia 1995 ; 209 : 60-63.
20. Erust I, Linner E, Svanborg A. CH rich fat poor diet in diabetes. Am J Med. 1965, 39 : 594-600.

21. Devod TC, Honoard Williams J, Thursfield V, Bron AJ et al DR : Diff. risk factors for exudates and h'ges, Int. ophthalmol 1986 ; 9 : 11-15.

22. Chantry K et al. Association of elevated serum lipid levels with retinal HE in DR. ETDRs report 22. Arch Ophthalmol 1996 ; 114 : 1079-1084.

23. Klein BE, Moss SE, Klein R, Suraroing R, The WESDR, XIII. Relationship of serum cholesterol to retinopathy and hard exudates. Ophthalmol 1991 ; 98 : 1261 – 1265.

24. Ditncon LT, Cullen JF et al. A 3 yr trial of atromid therapy in exudative DR. Diabetes 1968 ; 17 : 458-67.

25. Cullin JF, Ireland JT, Oliver MF. A controlled trial of Atromid therapy in exudative DR. Transophthalmol svc, UK 1964 ; 84 : 281-295.

26. Frycybourger H, Schifferdecker E, Schatz H. Regression of HE in diabetic background retinopathy in therapy with etofiltrate antilipaemic agent. Med Kein 1994 : 89 : 594-597.

27. Gordon B, Chang S, Karanagh M et al. The effect of lipid lowering on DR. Am J Ophthalmol 1991 ; 112 : 385-391.

28. Dale J, Farmer J, Jones AF et al. Diabetic ischaemic and exudative maculopathy ; are thin risk factors different ? Diab Med 2000 ; 17 : 47.

29. Dahl- Jorgensen K, Brinchmann- Hansen, O, Hanssen, KF, Sandvik, L, Aagenes, O, and the Aker Diabetes Group : Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes meelitus : the Oslo study, Br Med J 290 : 811-815, 1985.

30. Engerman, RL : Pathogenesis of diabetic retinopathy, Diabetes 38 : 1203 – 1206, 1989.

31. Engerman, RL, Davis, MD, and Bloodworth, JMB Jr : Retinopathy in experimental diabetes : its relevance to diabetic retinopathy in man. In Rodriguez, RR and Vallance-Owen, JR, eds : Diabetes, Amsterdam, 1971, Excerpta Medica.

32. Frank, RN, Hoffman, WH, Podgor, MJ, Joondeph, HC, Lewis, RA, Margherio, RR, Nachazel, DP Jr, Weiss, H, Christopherson, KW and Cronin, MA : Retinopathy in juvenile onset type 1 diabetes of short duration, ophthalmology 87 : 1-9, 1980.

33. Grunwald, JE, Brucker, AJ, Braunstein SN, Schwartz SS, Baker, L. Petrig, BL, and Riva, CE: Strict metabolic control and retinal blood flow in diabetes mellitus, Br J Ophthalmol 78 : 598-604, 1994.

34. Grunwald, JE, Brucker, AJ, Petrig, BL, and Riva, CE : Retinal blood flow regulation and the clinical response to parentinal photocoagulation in proliferative diabetic retinopathy, ophthalmology 96 : 1518-1522, 1989.

35. Kornerup T : Studies in diabetic retinopathy : an investigation of 1,000 cases of diabetes, Acta Med Scand 153 : 81-101 1955.

36. Arfken, CL, Salicrup, AE Meuer, SM et al : Retinopathy in African-Americans and whites with insulin-dependent diabetes mellitus, Arch Intern Med 154 : 2597-2602, 1994.

37. Berman DH, and Friedman, EA : Partial absorption of hard exudates to patients with diabetic end stage renal disease and severe anemia after treatment wit erythropoietin, Retina 14 : 1-5, 1994.

38. Chaturvedi N, Sjolie, AK, Stephen JM, Heidemarie, A, Deipes, M. Castellarin, A. Rogulja-Pepeonik, X, Fuller, JH

and the EUCLID. Study group : Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes, Lancet 351: 28-31, 1988.

39. Chew, EY, Klein, ML Ferris, FL, III, Remaley NA, Murphy RP, Chantry K Hoogwerf, BJ and Miller, D for the Early treatment Diabetic retinopathy Study Research, Group : Association of elevated serum lipid levels with retinal hard exudates in diabetic retinopathy. Arch Ophthalmol 114 : 1079-1084, 1996.

PROFORMA

Serial No. :

Name : Age : Sex :

OP. No. :

Duration of DM :

On Treatment :

Stage of DR : RE LE

No DR

Mild NPDR

Moderate NPDR

Severe NPDR

PDR

CSME RE LE

Investigations :

1. Fasting blood sugar (mg/dl)
2. Serum lipid profile
    a. Total cholesterol (mg / dl)
    b. Triglycerides (mg / dl)
    c. LDL – C (mg / dl)
    d. VLDL – C (mg / dl)
    e. HDL – C (mg / dl)
3. Blood Urea (mg / dl)
4. Serum creatinine (mg / dl)

Systolic Blood pressure

Diastolic Blood pressure

ABBREVIATIONS

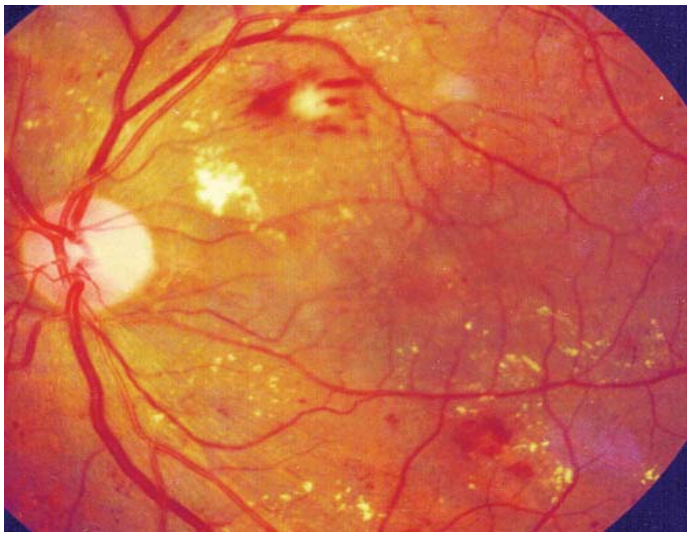
DM	DIABETES MELLITUS
DR	DIABETIC RETINOPATHY
NPDR	NON PROLIFERATIVE DIABETIC RETINOPATHY
PDR	PROLIFERATIVE DIABETIC RETINOPATHY
CSME	CLINICALLY SIGNIFICANT MACULAR EDEMA
DME	DIABETIC MACULAR EDEMA
LDL	LOW DENSITY LIPOPROTEIN
VLDL	VERY LOW DENSITY LIPOPROTEIN
HDL	HIGH DENSITY LIPOPROTEIN
TG	TRIGLYCERIDE
FBS	FASTING BLOOD SUGAR
ETDRS	EARLY TREATMENT DIABETIC RETINOPATHY STUDY
DCCT	DIABETICS CONTROL AND COMPLICATIONS TRIAL
UKPDS	UNITED KINGDOM PROSPECTIVE DIABETES STUDY
WESDR	WISCONSIN EPIDEMIOLOGIC STUDY OF DIABETIC RETINOPATHY

MODERATE NPDR WITHOUT CSME

PDR WITH HRC WITHOUT CSME

MODERATE NPDR WITH CSME

SEVERE NPDR WITH CSME



PDR WITH CSME

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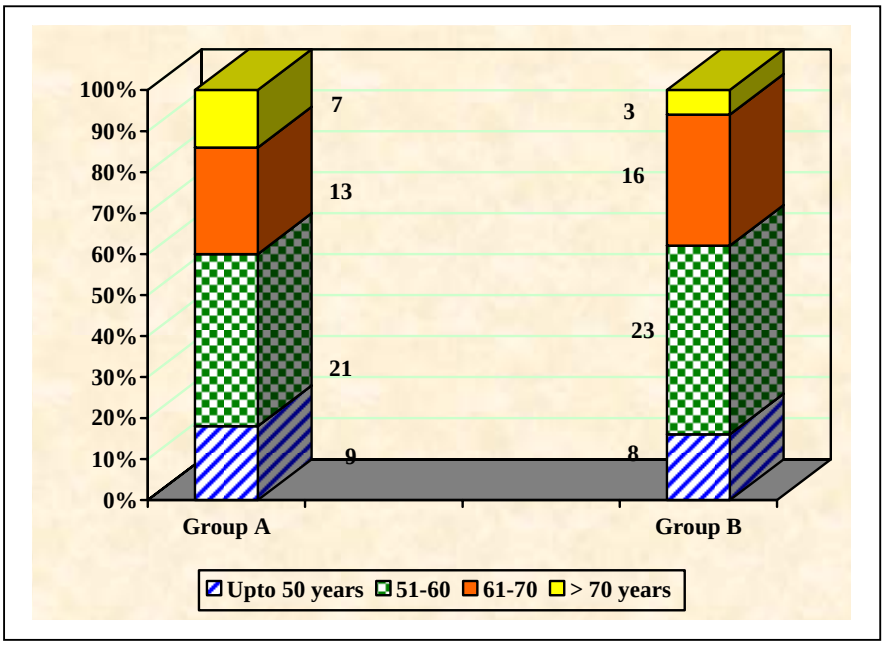

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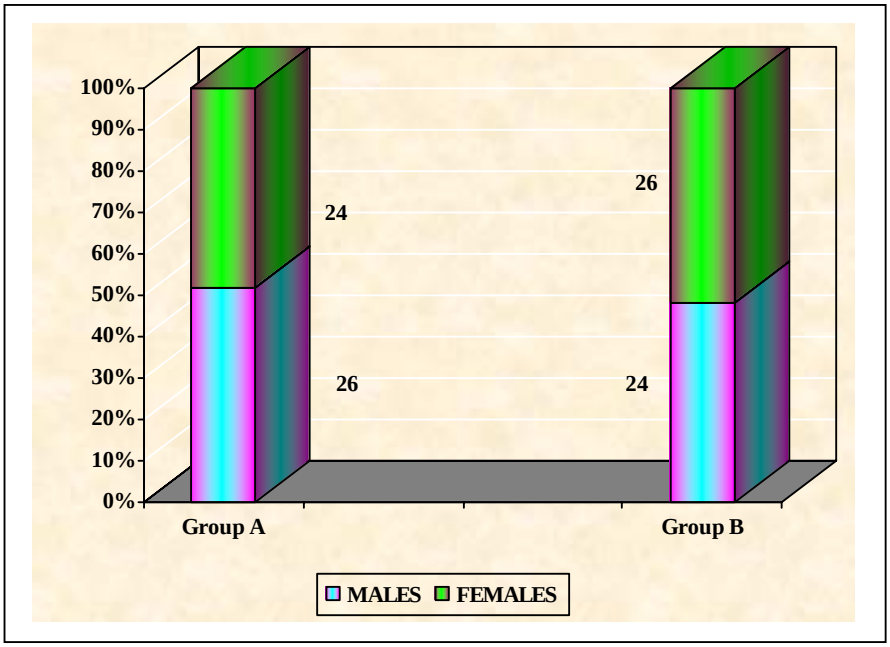

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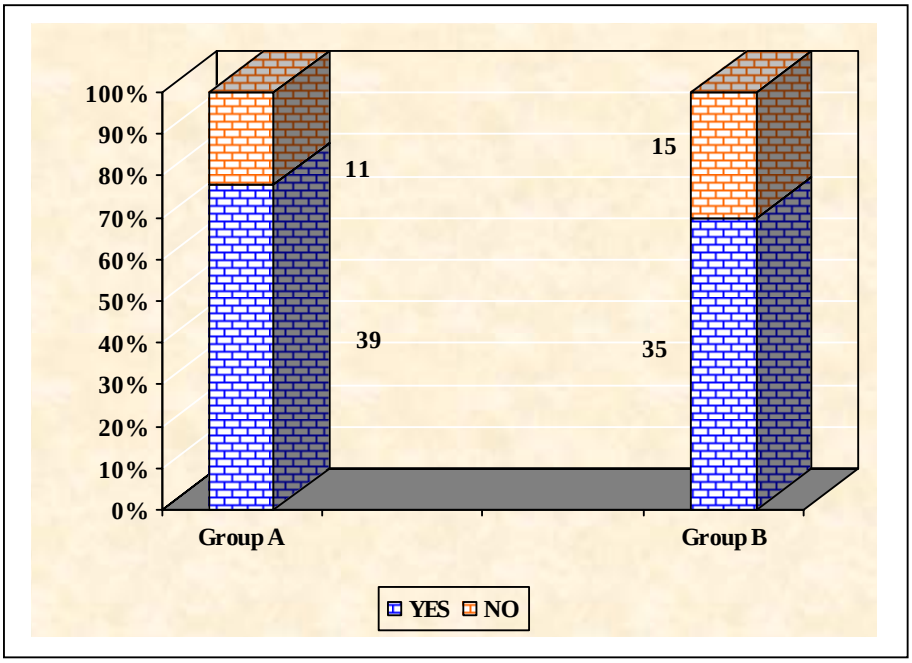

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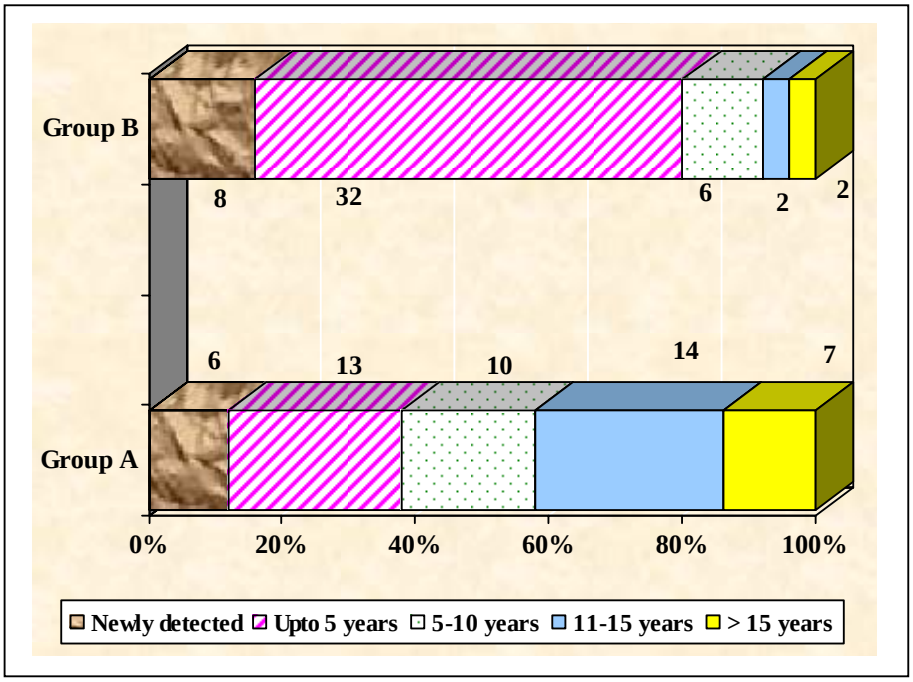

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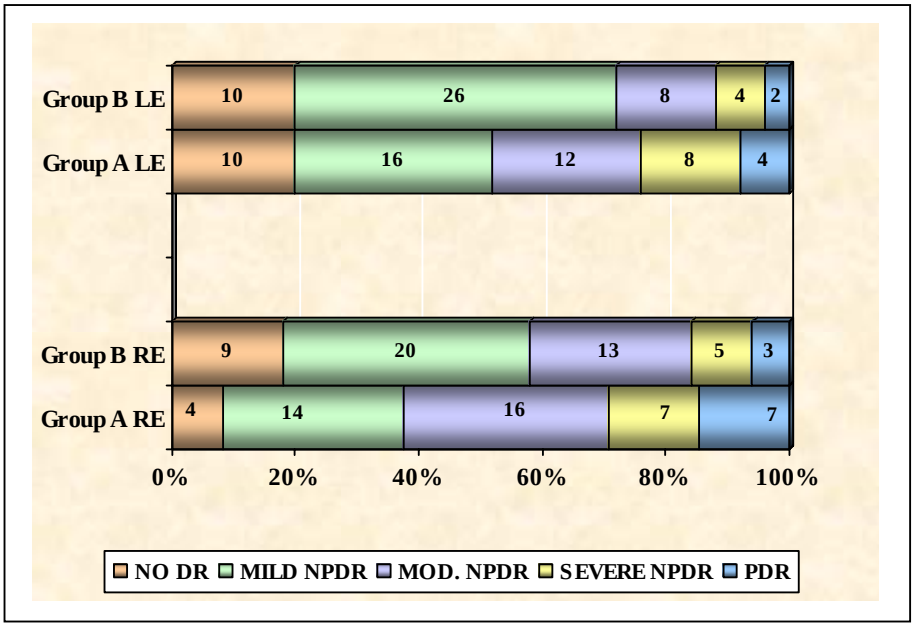

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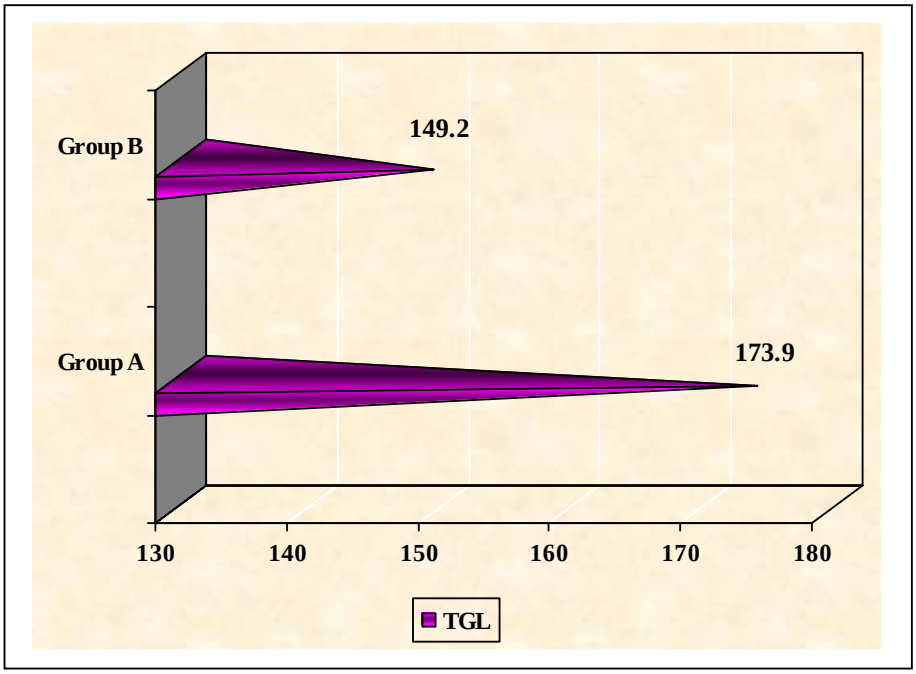

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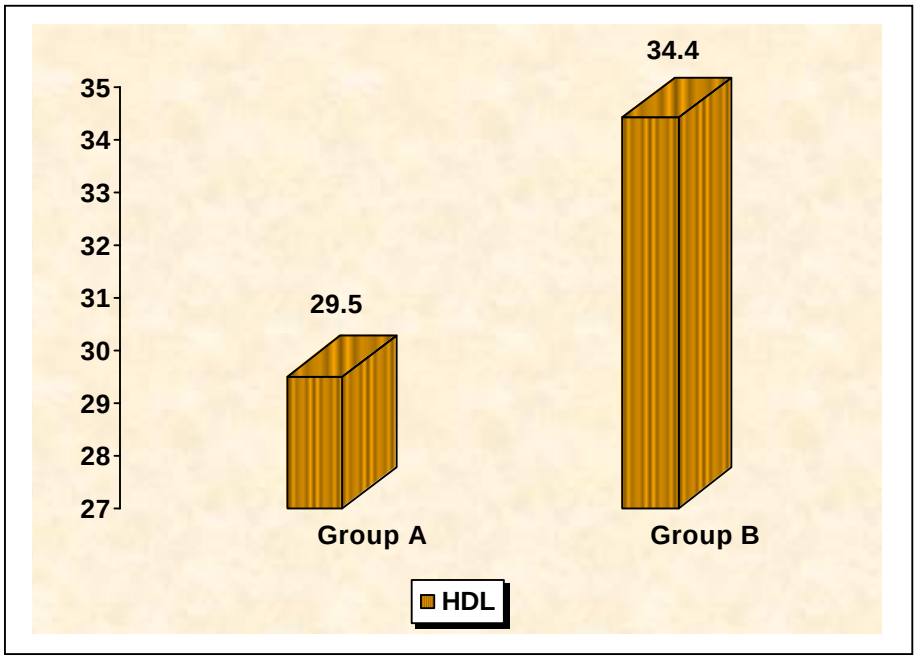
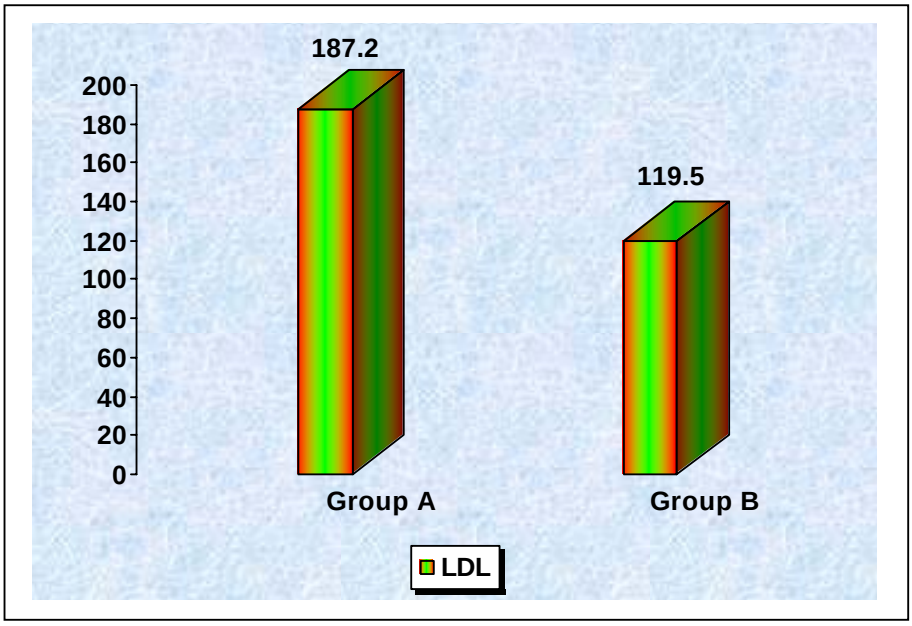
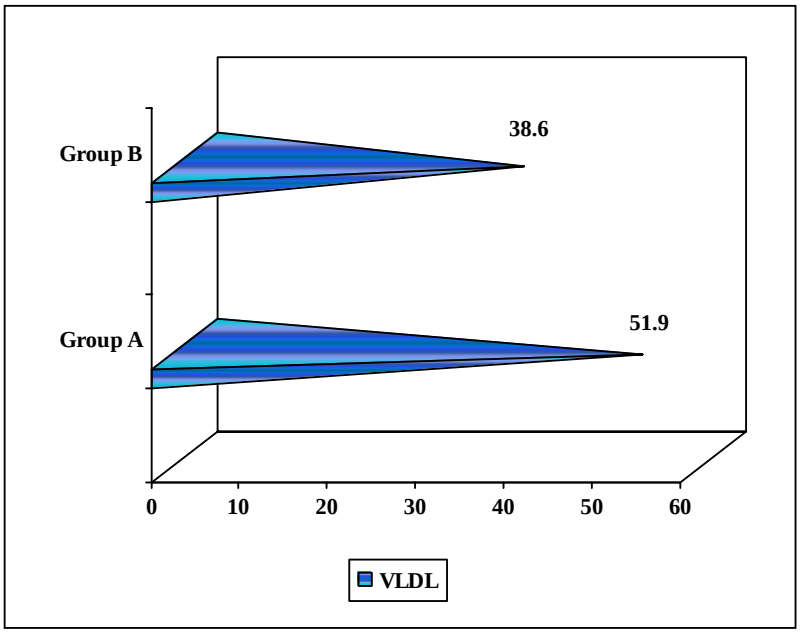


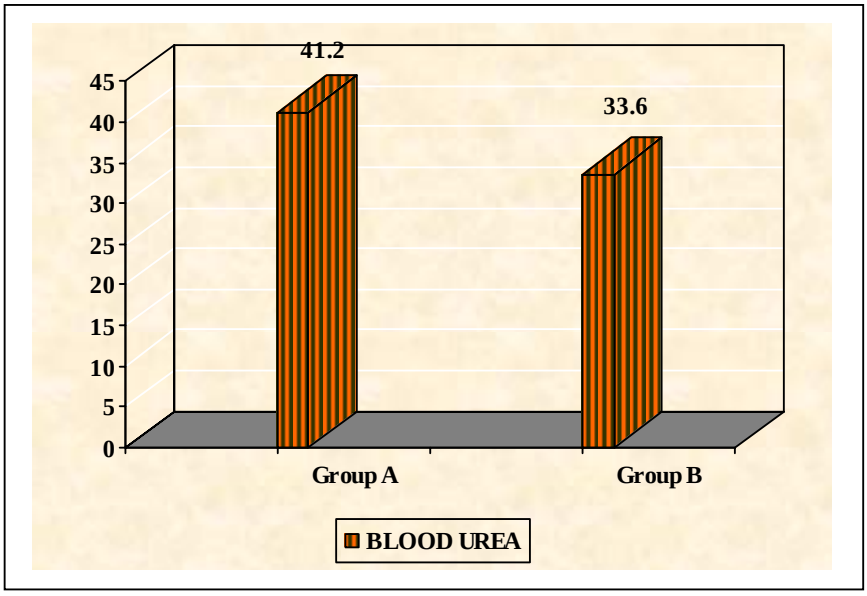
LDL & CSME


187.2
119.5
200
180
160
140
120
100
80
60
40
20
0
Group A
Group B
LDL

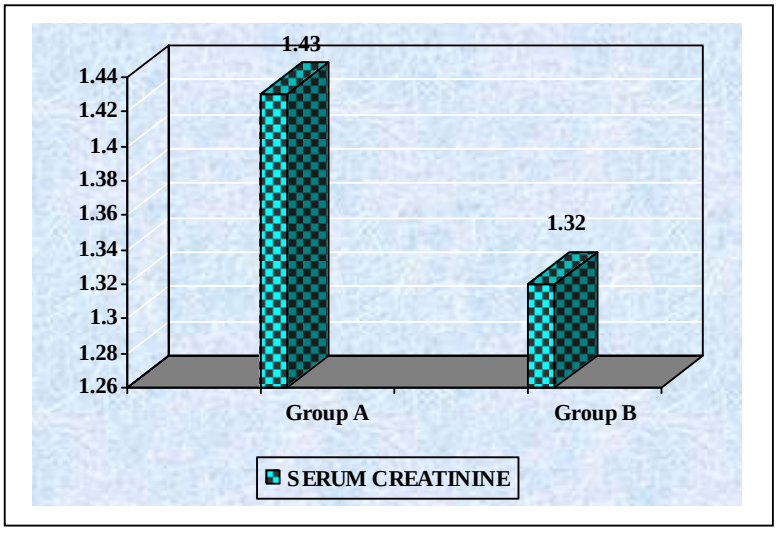
VLDL & CSME



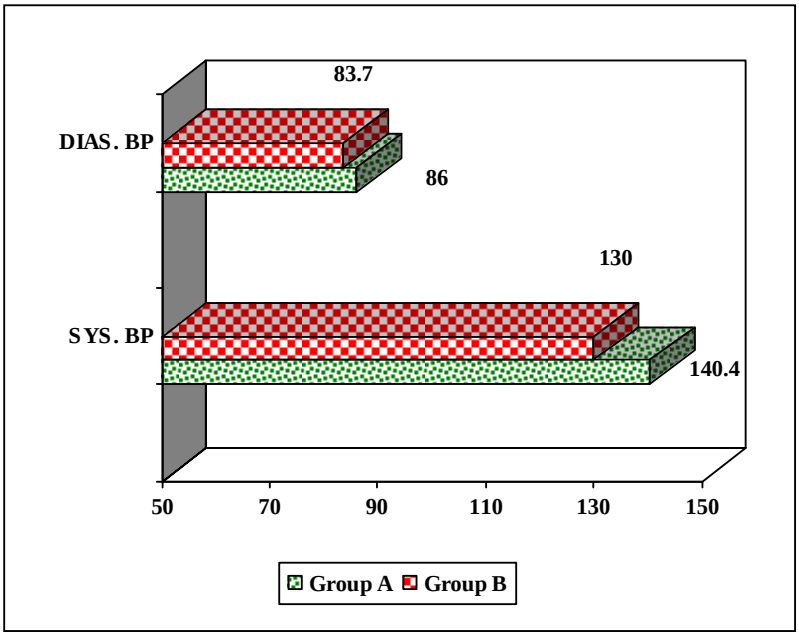
BLOOD UREA AND CSME



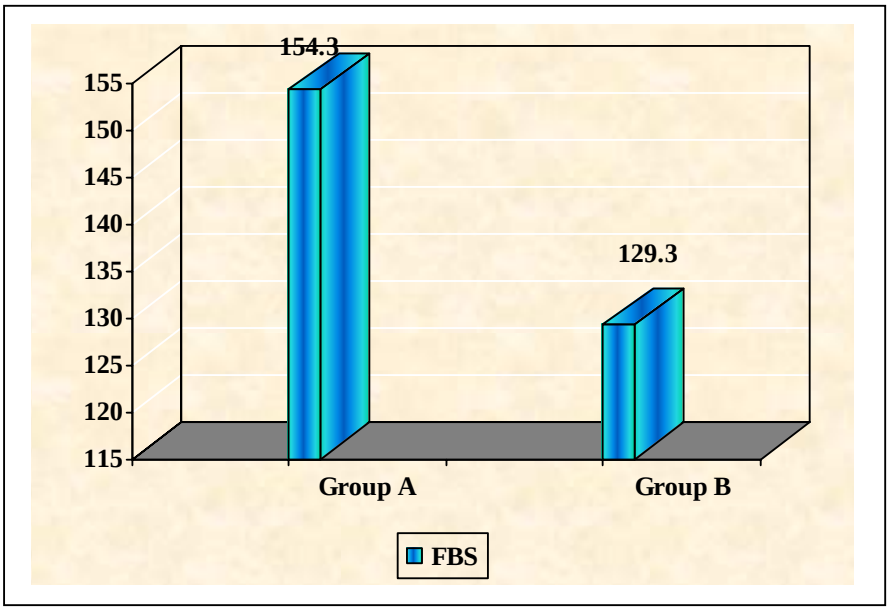
SERUM CREATININE AND CSME



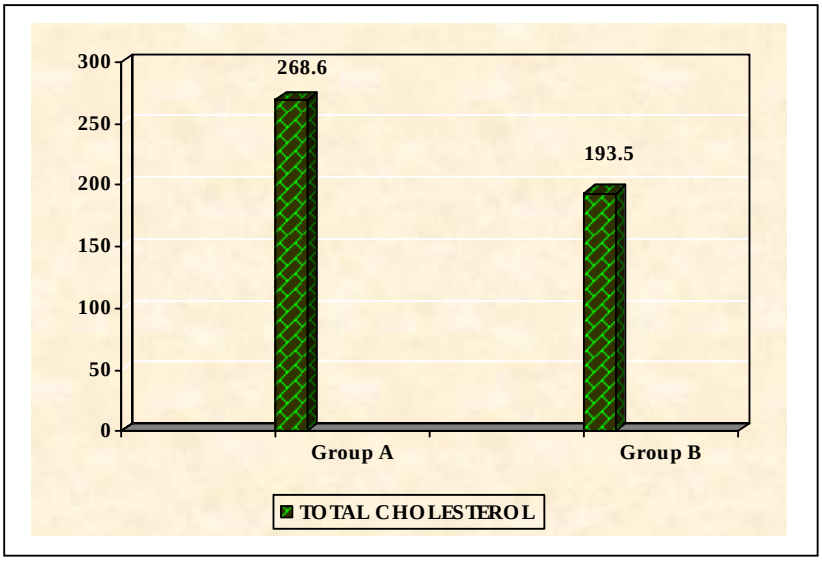
BLOOD PRESSURE AND CSME



FASTING BLOOD SUGAR AND CSME



TOTAL CHOLESTEROL & CSME



SERUM LIPID PROFILE OF PAITENTS WITH DIABETIC RETINOAPTHY WITH CSME

S. No.	name	age	sex	OP No	Duration of DM(yrs)	on drugs	STAGE OF DR		CSME		total cholesterol	triglycerides	HDL	LDL	VLDL	B.Urea	S.Creatinine	SBP	DBP	FBS
							RE	LE	RE	LE										
1	pethiammal	54	F	413246	7	Y	MILD NPDR	MOD. NPDR	N	Y	244	186	20	196	18	26	0.7	134	80	216
2	sarathy	64	M	414241	15	Y	SEV NPDR	PDR	Y	Y	414	214	26	348	40	70	3.2	150	96	284
3	kandasamy	44	M	414443	3	Y	MOD. NPDR	MOD. NPDR	Y	Y	196	174	14	154	28	32	0.9	120	76	119
4	dhanam	53	F	414819	ND	N	MILD NPDR	NO DR	Y	N	289	168	40	201	48	21	1.1	130	80	181
5	jayaram	54	M	414624	ND	N	NO DR	MOD. NPDR	N	Y	200	140	38	140	22	77	1.6	134	90	159
6	natarajan	60	M	414496	20	Y	PDR	MOD. NPDR	Y	Y	516	318	34	402	70	84	4.4	160	100	299
7	peer mohammed	68	M	414781	4	Y	MOD. NPDR	SEV NPDR	N	Y	140	123	12	122	16	19	1.2	136	76	112
8	rajammal	60	F	415612	11	Y	MILD NPDR	MILD NPDR	Y	Y	263	160	30	192	41	24	1.1	140	90	173
9	kathiresan	47	M	415723	13	Y	NO DR	MOD. NPDR	N	Y	164	144	35	110	19	44	1.2	154	90	134
10	maniammal	48	F	415946	4.5	Y	MOD. NPDR	MILD NPDR	Y	N	211	161	22	140	49	36	1	144	86	126
11	rajangam	51	M	416112	ND	N	MILD NPDR	SEV NPDR	Y	Y	319	169	31	220	68	51	1.3	140	80	130
12	vellathai	65	F	416114	11	Y	MOD. NPDR	MOD. NPDR	Y	Y	160	140	35	90	45	23	0.9	150	84	103
13	muthukani	75	F	416239	12	N	PDR	SEV NPDR	Y	Y	418	183	26	308	84	60	1.9	146	90	184
14	chinnan	53	M	415314	ND	N	MILD NPDR	NO DR	Y	N	324	167	41	219	64	48	1.4	150	84	126
15	shanmugavel	87	M	416491	5	Y	MILD NPDR	MILD NPDR	Y	N	281	157	28	193	60	40	1.3	148	90	116
16	ganesan	60	M	416423	1	Y	MOD. NPDR	NO DR	Y	N	190	130	30	130	30	27	1.1	140	84	108
17	selvaraj	73	M	416562	11	N	MOD. NPDR	MOD. NPDR	Y	Y	223	183	35	161	27	30	1.2	136	90	113
18	mary thomas	56	F	416621	4	Y	MILD NPDR	SEV NPDR	Y	Y	216	116	30	143	43	48	1.6	140	86	130
19	sandanam	49	M	416316	18	Y	MOD. NPDR	PDR	Y	Y	329	172	23	196	110	40	0.9	126	90	111
20	papammal	60	F	416813	6	Y	MOD. NPDR	MILD NPDR	N	Y	194	113	20	148	36	23	0.8	130	90	130
21	pandi	48	M	416916	2	Y	MILD NPDR	MILD NPDR	N	Y	442	243	38	300	104	46	1.3	140	84	116
22	gomathi	65	F	416844	1.5	N	SEV NPDR	MOD. NPDR	N	Y	346	176	56	212	78	21	1.1	146	80	149
23	pitchai	58	M	416992	ND	N	MILD NPDR	NO DR	Y	N	288	193	36	196	56	48	1.4	150	80	164
24	angammal	61	F	417231	17	Y	SEV NPDR	SEV NPDR	Y	Y	140	98	35	88	17	52	2.2	150	88	214
25	radha	57	F	417255	13	Y	MOD. NPDR	MILD NPDR	Y	Y	312	165	42	200	70	31	2	148	90	226
26	singaram	68	F	417367	8	Y	MOD. NPDR	NO DR	Y	N	194	143	26	150	18	21	0.8	130	94	126
27	sethulakshmi	65	F	417379	12	Y	PDR	MILD NPDR	Y	N	263	193	19	184	60	40	1.4	140	90	140
28	palanisamy	52	M	417413	9	Y	MILD NPDR	MILD NPDR	N	Y	299	174	19	211	69	36	1.2	130	80	182
29	chidambaram	71	M	417546	12	Y	MOD. NPDR	MILD NPDR	Y	Y	306	148	22	194	90	48	2.6	144	90	314

30	thangammal	60	F	417845	16	Y	SEV NPDR	MILD NPDR	Y	N	193	136	35	120	38	26	1.2	130	80	148
31	parameswari	57	F	418211	22	Y	PDR	PDR	Y	Y	391	204	39	281	71	34	2.4	140	90	284
32	venugopal	54	M	418348	ND	N	MILD NPDR	NO DR	Y	N	248	167	22	166	60	16	0.8	130	76	128
33	muniyandi	80	M	418446	11	N	MOD. NPDR	MILD NPDR	Y	N	144	140	35	84	25	40	1.3	126	80	140
34	balakrishnan	70	M	418325	35	Y	PDR	SEV NPDR	Y	Y	206	216	25	160	21	38	0.9	120	70	116
35	shanmugam	63	M	418416	10	Y	SEV NPDR	MILD NPDR	Y	N	218	161	24	164	30	37	1.2	140	80	84
36	alagu	62	M	418449	7	Y	MOD. NPDR	MOD. NPDR	Y	N	311	148	28	191	82	51	2.1	140	90	186
37	chandrasekar	55	M	418514	6	Y	MILD NPDR	MILD NPDR	Y	Y	385	264	36	269	80	70	2.6	138	86	164
38	kalimuthu	44	M	418566	3	Y	MILD NPDR	NO DR	Y	N	304	211	40	180	84	36	0.7	160	90	148
39	beevi jaan	66	F	418914	12	Y	MOD. NPDR	MOD. NPDR	Y	Y	216	254	24	166	30	49	1.2	148	90	136
40	rakku	60	F	418726	5	Y	NO DR	MILD NPDR	N	Y	180	113	30	130	20	20	0.6	130	82	104
41	rajammal	39	F	418839	21	Y	PDR	SEV NPDR	Y	Y	251	180	27	184	40	64	1.4	170	100	180
42	subramaniam	60	M	418214	8	Y	SEV NPDR	NO DR	Y	N	266	191	31	166	69	60	1.1	140	90	108
43	arokya mary	65	F	418865	11	Y	MILD NPDR	SEV NPDR	N	Y	199	142	30	140	25	31	0.9	120	70	116
44	ponnuthai	50	F	418931	1	Y	NO DR	MILD NPDR	N	Y	284	186	28	174	82	42	1.2	140	84	130
45	pushpavalli	54	F	418954	6	Y	MOD. NPDR	MILD NPDR	N	Y	318	200	44	221	53	48	1.6	150	90	211
46	ranganathan	48	M	419027	3.5	N	MOD. NPDR	NO DR	Y	N	277	193	23	194	60	50	1.3	130	80	140
47	rasuthevar	64	M	414621	9	Y	SEV NPDR	PDR	Y	Y	254	187	30	171	53	31	0.9	134	80	124
48	backiyam	72	F	419669	15	Y	MOD. NPDR	MOD. NPDR	N	Y	316	213	22	214	80	44	1.4	150	90	140
49	gandhimathi	74	F	419734	13	Y	PDR	MOD. NPDR	Y	Y	289	160	17	199	73	49	1.6	160	100	136
50	parvathy	60	F	419876	2	Y	MOD. NPDR	NO DR	Y	N	301	178	21	240	40	58	2.2	140	94	108

SERUM LIPID PROFILE OF PAITENTS WITH DIABETIC RETINOAPTHY WITHOUT CSME

S. No.	name	age	sex	OP No	Duration of DM(yrs)	on drugs	STAGE OF DR		CSME		total cholesterol	triglycerides	HDL	LDL	VLDL	B.Urea	S.Creatinine	SBP	DBP	FBS
1	vetrivel	57	M	416521	7	Y	MILD NPDR	MILD NPDR	N	N	192	197	42	111	39	21	1.1	120	80	180
2	ganesan	75	M	414461	4	Y	MOD. NPDR	MILD NPDR	N	N	142	156	38	83	21	40	1.3	130	84	126
3	karuppayee	55	F	413288	1	Y	NO DR	MILD NPDR	N	N	124	117	40	66	18	33	0.9	124	80	141
4	chinnavelu	65	M	415161	ND	N	MILD NPDR	NO DR	N	N	185	173	35	104	46	24	0.8	134	86	118
5	irulayee	54	F	416613	0.5	Y	MILD NPDR	MILD NPDR	N	N	144	132	40	71	33	28	1	110	70	143
6	subbaiah	70	M	416824	12	Y	SEV NPDR	MOD. NPDR	N	N	204	146	32	140	32	17	0.7	114	78	189
7	maideen beevi	60	F	416913	1.5	Y	MILD NPDR	MILD NPDR	N	N	196	173	20	145	31	23	0.9	120	82	214
8	sethukannan	62	M	417244	2	Y	MOD. NPDR	MILD NPDR	N	N	155	146	35	82	28	36	1.2	124	82	116
9	chandra	58	F	417153	20	Y	SEV NPDR	PDR	N	N	183	167	40	114	29	40	1.4	130	80	173
10	krishnan	67	M	417355	1	Y	NO DR	MILD NPDR	N	N	147	138	30	90	27	26	0.9	130	86	114
11	solamalai	45	M	417426	10	Y	SEV NPDR	MILD NPDR	N	N	316	261	30	169	62	18	0.7	140	88	81
12	masilamani	52	M	417538	3	Y	MILD NPDR	MILD NPDR	N	N	182	165	40	102	40	32	1	134	82	76
13	senthilmaran	61	M	417612	ND	N	MILD NPDR	NO DR	N	N	156	148	40	84	32	19	1	124	84	104
14	thangammal	68	F	417677	4	Y	MILD NPDR	MOD. NPDR	N	N	214	193	30	165	29	44	1.6	130	80	119
15	rajeshwari	42	F	417813	ND	N	MILD NPDR	MILD NPDR	N	N	163	165	36	82	45	24	1	116	70	65
16	krishnamoorthy	58	F	417968	ND	N	MOD. NPDR	NO DR	N	N	174	143	41	93	40	29	0.8	120	80	124
17	annakili	47	F	418114	2.5	Y	NO DR	MILD NPDR	N	N	116	97	40	54	22	36	0.9	130	90	142
18	nallathambi	61	M	418134	5	Y	SEV NPDR	MOD. NPDR	N	N	408	341	31	300	77	63	4.3	170	100	88
19	annamalai	72	M	418251	1	Y	MILD NPDR	MILD NPDR	N	N	158	153	44	74	40	21	0.8	140	90	83
20	sathayi	58	F	418299	1	N	MOD. NPDR	MILD NPDR	N	N	143	133	40	70	33	24	0.8	130	80	112
21	kaliammal	50	F	418316	2	N	NO DR	MILD NPDR	N	N	151	126	35	81	35	32	0.7	134	84	130
22	chinnathambi	70	M	418422	4	Y	MOD. NPDR	MOD. NPDR	N	N	284	214	30	198	56	43	2.1	140	100	172
23	jeyalatha	49	F	418483	3	Y	MILD NPDR	MOD. NPDR	N	N	177	168	36	110	31	36	0.9	120	80	118
24	annakodi	56	M	418517	1	N	NO DR	MILD NPDR	N	N	164	143	35	103	26	24	1.2	124	80	122
25	karuppaiah	59	M	418584	0.5	N	MOD. NPDR	MILD NPDR	N	N	183	162	40	116	27	25	1.1	130	86	124
26	saraswathi	65	F	418615	7	Y	MOD. NPDR	SEV NPDR	N	N	310	211	30	204	66	51	4	160	100	306
27	chellammal	62	F	418692	2	Y	NO DR	MILD NPDR	N	N	180	165	40	101	39	29	1.1	118	82	118
28	shanthi	53	F	418738	1	N	MILD NPDR	NO DR	N	N	137	113	40	56	42	34	0.8	120	84	51
29	venkatesan	56	M	418783	3	Y	MILD NPDR	MOD. NPDR	N	N	145	126	42	78	25	19	0.9	130	86	43

30	manjaiah	77	M	418816	15	Y	PDR	SEV NPDR	N	N	348	166	35	224	89	49	3.3	140	90	132
31	sornamma	70	F	418936	17	Y	PDR	PDR	N	N	233	168	22	179	31	36	1.1	130	80	48
32	kalavathi	51	F	418999	1	Y	MILD NPDR	MILD NPDR	N	N	174	132	38	106	30	38	1.2	114	70	71
33	muthupetchi	56	F	419000	6	Y	SEV NPDR	MILD NPDR	N	N	214	160	30	168	26	28	0.9	140	80	114
34	pethammal	50	F	419002	2	N	MILD NPDR	MILD NPDR	N	N	196	114	42	120	34	40	1.1	136	80	211
35	kuruvamma	59	F	419124	ND	N	MILD NPDR	NO DR	N	N	184	126	37	122	25	33	1.2	114	70	126
36	ramasamy	68	M	419361	9	Y	MOD. NPDR	NO DR	N	N	316	148	30	194	82	48	1.4	120	76	146
37	michael john	63	M	429473	3	Y	NO DR	MILD NPDR	N	N	114	104	35	60	9	26	0.8	130	86	65
38	kannan	56	M	419636	5	Y	MILD NPDR	MOD. NPDR	N	N	156	124	39	108	24	18	0.6	124	80	84
39	pandiammal	64	F	419715	1.5	Y	MILD NPDR	NO DR	N	N	148	118	30	82	36	24	0.9	130	90	128
40	bagyalakshmi	~~48~~	F	419777	ND	N	NO DR	MILD NPDR	N	N	129	84	28	68	33	36	0.9	120	80	106
41	muthammal	55	F	419818	0.5	Y	MOD. NPDR	MILD NPDR	N	N	143	93	35	74	34	42	1.4	124	90	112
42	vasantha	53	F	419863	2	Y	MILD NPDR	MILD NPDR	N	N	246	170	20	201	25	54	2.4	130	74	130
43	sayeeda begum	60	F	419934	9	Y	PDR	MOD. NPDR	N	N	400	212	30	240	130	70	4.3	140	100	184
44	veerakalai	64	M	419985	5	N	MOD. NPDR	SEV NPDR	N	N	312	194	24	190	98	63	2.6	170	106	126
45	thalaimalai	60	M	420017	1	Y	MOD. NPDR	NO DR	N	N	134	76	35	84	25	29	1.1	140	90	214
46	ottammal	63	F	420164	3	Y	MOD. NPDR	SEV NPDR	N	N	116	101	23	73	20	32	1	120	80	114
47	kasimayan	59	M	420178	ND	N	MILD NPDR	NO DR	N	N	188	112	40	121	27	48	1.2	140	94	143
48	mahalingam	53	M	420344	1	Y	MILD NPDR	MILD NPDR	N	N	163	83	24	108	31	33	0.8	134	80	189
49	nagarathinam	55	F	420561	2	Y	MOD. NPDR	NO DR	N	N	148	99	36	83	29	24	0.8	130	80	209
50	mookan	48	M	420715	ND	N	NO DR	MILD NPDR	N	N	180	104	35	124	21	19	0.9	126	76	120